

PRELIMINARY AMENDMENT

Serial Number: Unknown

Filing Date: Herewith

Title: CEA/NCA-BASED DIFFERENTIATION CANCER THERAPY

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Dkt: 186.009US1

14. (NEW) A method for selecting a peptide or peptide-derived mimetics which can modulate a differentiation-blocking activity associated with a subdomain of CEA/NCA in a malignant tumor, wherein said subdomain is selected from the group consisting of sequences G₃₀YSWYK; N₄₂RQII; Q₈₀ND; sequences including epitopes of 3 to 6 amino acids in the N-terminal 107 amino acid domain; and sequences including epitopes of 3 to 6 amino acids in the internal A3B3 178 amino acid domain of CEA, wherein said peptide or peptide-derived mimetics is selected as a modulator of said differentiation-blocking activity, when a tumor cell incubated with said peptide or peptide-derived mimetics, displays a significantly modified differentiation status as compared to a tumor cell incubated in the absence thereof.

15. (NEW) Peptides and/or peptide-derived mimetics obtained by the method of claim 14, wherein said peptide and peptide-derived mimetics interacting with subdomains of CEA/NCA involved in the differentiation-blocking activity associated with malignant tumors, wherein said subdomains are selected from the group consisting of sequences G₃₀YSWYK, N₄₂RQII, and Q₈₀ND.

16. (NEW) A shankless anchor, which comprises a GPI anchor of CEA without the external domains thereof, wherein said GPI anchor interferes with downstream targets of endogenous CEA/NCA molecules to inhibit a differentiation-blocking activity thereof when administered to a primary or secondary tumor cell.

17. (NEW) A method to restore endogenous integrin function, which comprises: an administration of a monoclonal antibody (MAB) that reverses a CEA/NCA-induced change in integrin function; or an administration of a peptide or peptide-derived-mimetic that mimics an effect of said MAB; thereby inhibiting a differentiation-blocking activity of endogenous CEA/NCA molecules.

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18. (NEW) The method of claim 17, wherein said integrin function includes integrins $\alpha_5\beta_1$ and $\alpha_v\beta_3$.

19. (NEW) A drug screen assay to select a pharmaceutical agent which is capable of inhibiting a differentiation-blocking activity of endogenous CEA/NCA molecules in a cell, which comprises, an incubation of said cell with a candidate agent, wherein said pharmaceutical agent is selected when said differentiation-blocking activity is significantly inhibited in the presence of said candidate agent as compared to in the absence thereof.

20. (NEW) A method for enhancing efficacy of a cytotoxic drug by increasing the differentiation status of tumor cells and/or by enhancing bystander effect, whereby more differentiated tumor cells cause adjacent autonomous tumor cells to behave more as non-malignant or normal cells, said method comprising an incubation of said tumor cells with an agent which interferes with one of a subdomain of CEA/NCA selected from the group consisting of sequences G₃₀YSWYK, N₄₂RQII, and Q₈₀ND, and an integrin selected from the group consisting of $\alpha_5\beta_1$ and $\alpha_v\beta_3$, thereby increasing said differentiation status and enhancing said efficacy of said drug.

21. (NEW) The method of claim 14, wherein said subdomain is selected from the group consisting of sequences G₃₀YSWYK, N₄₂RQII, and Q₈₀ND.

22. (NEW) The method of claim 19, wherein said cell is a rat L6 myoblast expressing CEA/NCA.

23. (NEW) The method of claim 19, wherein said cell is a human Caco-2 colonocyte which aberrantly expresses a high level of CEA/NCA, and wherein said inhibition of differentiation-blocking activity can be positively correlated with a restoring of normal cellular and tissue architecture of said Caco-2 cells, upon incubation with said pharmaceutical agent.

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24. (NEW) The method of claim 20, wherein said agent is selected from the group consisting of:

- a) anti-CEA/NCA antibodies which specifically interact with a subdomain of CEA/NCA selected from sequences G₃₀YSWYK, N₄₂RQII, and Q₈₀ND;
- b) a peptide having a sequence selected from G₃₀YSWYK, N₄₂RQII, and Q₈₀ND;
- c) a peptide mimetic of b);
- d) an antisense of CEA/NCA; and
- e) a shankless anchor of CEA/NCA comprising a GPI anchor of CEA without the external domains thereof.

25. (NEW) A method of relieving a CEA/NCA-imposed inhibition of differentiation and/or apoptosis comprising an incubation of primary or secondary tumor cells with an agent which disrupts one of an interaction between CEA/NCA subdomains having sequences selected from G₃₀YSWYK, N₄₂RQII, and Q₈₀ND, and a functional interaction between said subdomains and integrin $\alpha_5\beta_1$ and $\alpha_v\beta_3$.

REMARKS

Claims 1 through 11 have been canceled and claims 12-25 have been newly added.

Claims 12-25 are currently pending.

Respectfully submitted,

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Date August 11, 2000

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Express Mail® mailing label number: EL600376098US

Date of Deposit: August 11, 2000
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